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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/238,972 | 01/27/99 | MACLEOD C | D5232CIP3 |

| EXAMINER | |
|---|---|
| WANG, A | |
| ART UNIT | PAPER NUMBER |
| 1635 | 4 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

FILE COPY

| Office Action Summary | Application No. 09/238,972 | Applicant(s) MacLeod |
|---|---|---|
| | Examiner Andrew Wang | Group Art Unit 1635 |

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) *10-15 and 18-20* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9, 16, and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The computer and paper copy of the sequence listing filed January 27, 1999 has been approved and entered.

### *Election/Restriction*

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-9, 16, and 17, drawn to antisense oligos and methods of treatment using said oligos, classified in class 514, subclass 44.

II. Claims 10-15, drawn to antibodies and methods of treatment using said antibodies, classified in class 424, subclass 130.1.

III. Claims 18-20, drawn to transgenic animals and methods of using said animals, classified in class 800, subclass 3.

3. The inventions are distinct, each from the other because of the following reasons: Inventions I and II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions, I and II, have different modes of operation since antibodies bind antigens and antisense

oligos bind nucleic acids. Moreover, inventions I and II are unrelated to III since the methods of treatment cannot be used in making a transgenic animal.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Benjamin Adler on April 5, 1999 a provisional election was made with traverse to prosecute the invention of I, claims 1-9, 16, and 17. Affirmation of this election must be made by applicant in replying to this Office action. Claims 10-15, and 18-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicants' C-I-P priority claim to application 08/187,634, which is a C-I-P of 07/686,322, which is a C-I-P of 07/509,684, has not been granted since no support for antisense oligos could be found in parent application 08/187,634, now U.S. Patent No. 5,866,123. Although support for antisense oligos could be found in 07/686,322, now U.S. Patent No. 5,312,733, priority was not granted since application '322 was not co-pending with the presently filed application 09/238,972. Moreover, application '634 did not incorporate the contents of application '322 by reference thereby preventing priority status to the filing date of application

'322. Therefore, this application, more specifically claims 1-9, 16, and 17, has received priority only to the filing date of the present application, which is January 27, 1999.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 3, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,312,733 (MacLeod).

The invention of the above claims is drawn to any antisense oligo which inhibits CAT2 translation and also to an antisense oligo having SEQ ID NO:2.

MacLeod discloses the CAT2 cDNA double stranded sequence identified as SEQ ID NO: 5, which embraces SEQ ID NO: 2, and also discloses that antisense sequences can be used to inhibit CAT2 translation (paragraph bridging columns 3-4).

Therefore, the invention of the above claims have been anticipated by MacLeod.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to any antisense oligo which inhibits CAT2 translation and pharmaceutical compositions comprising said antisense oligo.

The specification describes the inhibitory activity of an antisense oligo consisting of SEQ ID NO: 2 and shows that administration of said oligo to Xenopus oocytes comprising polyA+ CAT2 mRNA resulted in restoring L-arginine transport to normal levels as compared to a control oligo (SEQ ID NO: 1).

No other antisense oligos targeted to any other regions of the CAT2 RNA that exhibited inhibitory activity are disclosed nor does the specification provide adequate description of a pharmaceutical composition comprising an antisense oligo targeted to CAT2 RNA.

Thus, the specification as filed fails to provide sufficient written description for any antisense oligo targeted to CAT2 RNA other than SEQ ID NO: 2. It should be noted that the searched prior art appears to be free of the claimed antisense oligo and therefore provides little guidance, in addition to the specification, that would allow the skilled artisan to find, obtain, or envision any other antisense oligo that is capable of inhibiting CAT2 RNA thereby disrupting translation of cationic amino acid transport protein since the inhibitory activity of any antisense oligo cannot be determined based solely on its primary structure. Moreover, the specification

provides no description or guidance as to any pharmaceutical compositions comprising the antisense oligo since no evidence is provided demonstrating the ameliorative effects of treatment with said antisense oligo.

Without such guidance and in view of what was known in the art, the disclosure is not sufficient to describe the claimed genus of antisense oligos targeted to CAT2 RNA and pharmaceutical compositions comprising said oligos.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112, paragraph, "Written Description" requirement.

9. Claims 1-9 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to an antisense oligo consisting of SEQ ID NO:2 and a method of inhibiting CAT2 expression using said antisense oligo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is drawn to any antisense oligo targeted to CAT2 mRNA and methods of treatment for diseases involving nitric oxide including sepsis, neoplastic disease, autoimmune disease, cachexia, cerebral malaria, cardiovascular disease, cerebrovascular disease, capillary leak syndrome, systemic lupus, erythematosus, rheumatoid arthritis, multiple sclerosis, breast cancer, and lung cancer.

The specification teaches the inhibitory activity of an antisense oligo consisting of SEQ ID NO: 2 and shows that administration of said oligo to Xenopus oocytes comprising polyA+ CAT2 mRNA resulted in restoring L-arginine transport to normal levels as compared to a control oligo (SEQ ID NO: 1). Moreover the specification teaches that CAT2 is involved in arginine transport which was shown to be essential in nitric oxide synthesis. In addition, iNOS expression was shown to be correlative with mammary tumorigenesis since mice with a functional iNOS gene developed mammary tumors more rapidly than iNOS knockout mice. The specification does not provide any guidance regarding the administration of any type antisense oligo targeted to CAT2 that would result in an ameliorative effect of any particular pathological state nor does the specification provide sufficient guidance that would enable a skilled artisan to treat a pathological condition by inhibiting CAT2.

The specification gives no guidance to enable a skilled artisan to use an antisense oligo in a method of treating any disease by administering said antisense oligos since the instant specification does not provide any guidance for an antisense oligo that would prove to be effective in the treatment of a pathological condition. Although the specification provides guidance on a singular antisense oligo (SEQ ID NO: 2), it is well known by those skilled in the art that identification of target sites in a given mRNA at which antisense oligos bind to cause inhibition of translation is an unpredictable art. The skilled artisan would recognize that careful screening of oligos targeted to different sites on a given mRNA to find oligo binding sites for inhibition of translation, may fail to identify such sites in the 5' untranslated region, the coding region, or in the 3' untranslated region

of the mRNA and that an oligo binding site that is located only a few bases to either side of an unsuccessful target site may give very effective inhibition of translation (Hoke *et al.*, column 9 and Table 1). In a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161, second and third columns). This point is further expounded by Branch, who states that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column).

The clinical application of antisense is also questioned since there are several obstacles that must be overcome such as degradation, molecular size and charge, bioavailability, toxicity, etc... as evidenced by Rojanasakul (abstract) who gives evidence that the use of antisense oligonucleotides in vivo caused renal failure due to toxicity of the antisense oligonucleotide which could be due to nonspecific effects of the oligo itself (page 118, second column, first paragraph). Branch further elucidates this point by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (page 46, second column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161,

second and third columns). Gewirtz *et al.* and Branch conclude by observing that, "the antisense approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph) and "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, these effects must be explored on a case-by-case basis." (page 50), respectively.

Therefore, as discussed above in detail a skilled artisan would have had to engage in undue trial and error experimentation to resolve that difficulties, as discussed above, to have had practiced the invention as claimed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew Wang whose telephone number is (703) 306-3217. The examiner can normally be reached on Monday to Thursday from 7:00 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NANCY DEGEN
PRIMARY EXAMINER

Andrew Wang
April 6, 1999